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10/567,320	08/18/2006	John W. Hadden	3115.00083	6669

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EXAMINER	
WEN, SHARON X	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,320	HADDEN, JOHN W.	
	Examiner	Art Unit	
	SHARON WEN	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 02/08/2010, has been entered.

Claims 1-13 and 16-32 have been canceled.

Claims 14-15 are currently pending and are currently under examination as the claims are directed to a method of immunotherapy to treat cancer by administering an effective amount of cyclophosphamide (CY) in combination with an effective amount of indomethacin (INDO) and an effective amount of cytokines consisting of IFN-γ, IL-2, IL-1, and TNF-α.

2. This Action will be in response to Applicant's Arguments/Remarks, filed 02/08/2010.

The rejections of record can be found in the previous Office Actions, mailed 02/20/2008, 12/22/2008 and 08/06/2009.

3. Applicant's sequence listing, submitted 02/08/2010, has been entered. The previous objection regarding the defective sequence has been withdrawn.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 14 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meneses et al. (*Arch. Pathol. Lab. Med.* 1998, 122:447-454, reference of record) in view Nohria et al. (*Biotherapy* 1994, 7:261-269).

Applicant's argument has been considered but has not been found convincing for reasons of record and reiterated herein for Applicant's convenience.

Meneses et al. taught a method of immunotherapy to treat head and neck squamous cell carcinoma (H&NSCC) comprising administering an effective amount of CY and INDO and a cytokine mixture comprised of IL-1, IL-2, TNF-α, and IFN-γ (see, e.g., page 447, Abstract "Patients" and page 448, Material and Methods, "Natural Cytokine Mixture" and "IRX-2 Treatment Schedule").

The difference between Meneses et al. and the present claims is that Meneses's cytokine mixture is **comprised** of IL-1, IL-2, TNF-α, and IFN-γ not **consisting of** IL-1, IL-2, TNF-α, and IFN-γ as recited in the present claims. However, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to pick the four cytokines recited in the claims from the cytokine list taught by Meneses et al. because it would have been obvious for the ordinary artisan to a particular combination of cytokines by selecting from a finite number of identified, predictable solutions, with reasonable expectation of success.

The rationale to support a conclusion that the claims would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. the finite number of cytokines taught by the prior art used in immunotherapy for treating cancer) within his or her technical grasp. This leads to the anticipated success of treating cancer with IL-1, IL-2, TNF-α, and IFN-γ in the absence of other cytokines taught by Meneses. It is likely the product not of innovation but of ordinary skill and common sense.

Furthermore, using cytokines in immunotherapy has long been recognized as part of the ordinary skill of the artisan at the time the invention was made as evidenced by Nohria et al. (see entire document). In particular, Nohria taught that cytokines are attractive as potential immunomodulators in immunotherapy for immunosuppressed patients because they can be made **recombinantly** thus making them abundantly available (see page 262, right column, first paragraph). Furthermore, Nohria et al. taught that the use of cytokines may allow one to selectively enhance particular immune parameters that are needed to optimize the immunotherapy. Upon reading Nohria, one of ordinary skill in the art would have been reasonably expected to try different combination of cytokines taught by Meneses et al. for the purpose of optimizing the particular immune parameter needed for treating patients with head and neck squamous cell carcinoma.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). Here, the result effective variable is the different cytokine combinations chosen from the finite list of cytokines taught by Meneses et al. One of ordinary skill in the art would have been motivated to try different combinations of cytokines in order to fine one that optimizes the particular immune parameter that needed to be optimized for treating patients with head and neck squamous cell carcinoma. It is also within his / her technical grasp to try these different cytokine combinations chosen from the finite choices of the cytokines taught by the prior art, with reasonable expectation of success because these cytokines were known to have immune-

activating activity as taught by Nohria et al. (see sections under *Interleukin-1*, *Interleukin-2*, *Tumor necrosis factor* and *Gamma-Interferon* on pages 262-266).

Therefore the particular combination of cytokines recited in the instant claims (i.e., IL-1, IL-2, TNF-α, and IFN-γ) were obvious at the time the invention was made given that it is a well-known practice to optimize result-effective variables such as a particular cytokine combination for a particular immune parameter in immunotherapy as taught by Nohria et al.

In view of the clear teachings of the prior art to use a cytokine mixture for treating cancer in conjunction with routine laboratory optimization of immune parameter with a particular cytokine combination, it would have been obvious to a person of ordinary skill in the art, at the time of invention, to select IL-1, IL-2, TNF-α, and IFN-γ from the finite list of cytokines taught by Meneses et al. for immunotherapy for treating cancer.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues the following:

Meneses, et al. teaches the use of a cytokine mixture that includes IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, TNF-α, CSF, and IFN-γ. Meneses, et al. does not express any criticality to any of the cytokines used in the mixture. Furthermore, Meneses, et al. states that IL-2 alone was shown to cause cancer recurrence with little clinical activity. Nohria, et al. also does not state that any particular cytokine is better than another. Thus, comparing the composition of Meneses, et al. versus what was known in the prior art, each of the cytokines would be expected to be necessary to perform a certain function. It would not be expected that fewer cytokines would provide as good of a response as the composition of Meneses, et al. Therefore, it is unexpected that the critical cytokines of IL-1, IL-2, TNF-α and IFN-γ, alone without the presence of other cytokines can be used as an effective treatment for cancer.

In response to Applicant's assertion that Meneses stated that IL-2 alone was shown to cause cancer recurrence, it is noted that Meneses clearly taught a mixture of cytokines (IRX-2) that includes IL-1, IL-2, TNF-α and IFN-γ (see page 448, section Natural Cytokine Mixture). The fact that Meneses did not specifically express critically of each cytokine used does not discourage one of ordinary skill in the art to try different combinations of cytokines for the purpose of optimizing the particular immune parameter as Norhria has taught that the use of cytokines may allow one to selectively enhance particular immune parameters that are needed to optimize the immunotherapy.

Given that Meneses taught the cytokines were useful for reducing tumor, it would have been obvious to one of ordinary skill in the art to try different combinations of cytokines choosing from a finite number of identified cytokines taught by Meneses that represent predictable solutions, with reasonable expectation of success.

It appears that Applicant argues unexpected result in the assertion that it would not be expected that fewer cytokines than those taught by Meneses would provide as good of a response. However, Applicant has not provided any evidence or point to where in the specification as-filed that would support Applicant's assertion. It is noted that attorney argument, absent supporting evidence, is entitled to little, if any, weight. *Velander v. Garner,* 348 F.3d 1359, 1371, (Fed. Cir. 2003); *Meitzner v. Mindick,* 549 F.2d 775,782, (CCPA 1977).

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. administration of a cytokine mixture to treat cancer and to boost immune response as taught by Meneses / optimizing result-effective variables such as a particular cytokine combination for a particular immune parameter in immunotherapy as taught by Nohria) within his or her technical grasp. This leads to the anticipated success of treating cancer with a particular mixture of cytokine selected from those taught in the prior art. It is likely the product not of innovation but of ordinary skill and common sense.

Applicant's argument has been considered in full but has not been found convincing for reasons of record. Therefore, the rejection is hereby maintained.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 14-15 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-9 of U.S. Patent No. 6,977,072 ('072) in view Nohria et al. (*Biotherapy* 1994, 7:261-269).

Applicant's willingness to provide the appropriate terminal disclaimer upon allowance of the pending claims has been acknowledged. However, the present claims stand rejected for reason of record. The rejection of record is reiterated below for Applicant's convenience.

> Both sets of claims are drawn to the method of treating cancer comprising administering CY and INDO and a cytokine mixture. Claims of patent '072 differ from claims of the present application in that the cytokine mixture is not exclusive to IL-1, IL-2, TNF-α, and IFN-γ. However, it would have been obvious to one of ordinary skill in the art to pick IL-1, IL-2, TNF-α, and IFN-γ from the cytokine list recited in the claims of patent '072 because it would have been obvious for the ordinary artisan to try by choosing from a finite number of identified, predictable solutions, which reasonable expectation of success in view of Nohria et al.
>
> In particular, Nohria taught that cytokines are attractive as potential immunomodulators in immunotherapy for immunosuppressed patients because they can be made **recombinantly** thus making them abundantly available (see page 262, right column, first paragraph). Furthermore, Nohria et al. taught that the use of cytokines may allow one to selectively enhance particular immune parameters that are needed to optimize the immunotherapy. Upon reading Nohria, one of ordinary skill in the art would have been reasonably expected to try different combinations of cytokines chosen from the finite number of the cytokines recited in the claims of the patent for the purpose of optimizing the particular immune parameter needed for cancer immunotherapy. Therefore, the claims of the patent render obvious of the claims of the present application.

8. Claims 14-15 stand *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following:

A) claims 1-3, 11, 16-18 and 20-21 of copending application USSN 11/582,063;

B) claims 44-45, 48 and 52-54 of copending application USSN 11/374,783;

C) claims 38-42 and 52-62 of copending application USSN 11/337,358; and

D) claims 1-3, 8-9, 17-18 and 20-22 of copending application USSN 11/006,451.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the above mentioned claims of the co-pending applications and the claims of the present application are both drawn to a method of treating cancer comprising administering CY, INDO and a cytokine mixture. Although the claims of the co-pending applications do not recite the particular cytokine combination as claimed in the present application, (i.e., IL-1, IL-2, TNF-α, and IFN-γ), it would have been obvious to one of ordinary skill in the art to select these cytokines from the finite list of cytokines recited in the claims of the co-pending applications for reasons stated above (see above 103 rejection and obviousness-type double patenting rejection against patent '072 for full analysis).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's willingness to provide the appropriate terminal disclaimer upon allowance of the pending claims has been acknowledges. However, the present claims stand rejected for reason of record as reiterated above for Applicant's convenience.

Conclusion

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON WEN whose telephone number is (571)270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571)272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Wen/
Examiner, Art Unit 1644
May 17, 2010

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649

/George C. Elliott, Ph.D./
Director, Technology Center 1600